ORGANIC LETTERS

2010
Vol. 12, No. 7
1516−1519

Transition-Metal-Free Electrophilic Amination between Aryl Grignard Reagents and *N*-Chloroamines

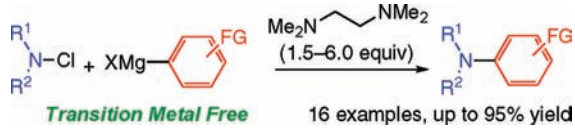
Takuji Hatakeyama,[†] Yuya Yoshimoto,[†] Sujit K. Ghorai,[†] and Masaharu Nakamura*,[†]

International Research Center for Elements Science, Institute for Chemical Research, and Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Uji, Kyoto, 611-0011, Japan

masaharu@scl.kyoto-u.ac.jp

Received January 29, 2010

ABSTRACT



In the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as an additive, easily prepared and handled *N*-chloroamines react with aryl Grignard reagents to give a variety of arylamines in good to excellent yields. Functional groups such as ester and nitrile are compatible under the reaction conditions.

Aromatic carbon−nitrogen bond formation is an important class of synthetic organic transformation.[1] In the past two decades, the Buchwald−Hartwig coupling[2] based on palladium,[3] copper,[4] or nickel[5] catalysis has been intensively developed into a wide-spread method for the synthesis of functional arylamines, which are of particular interest in organic electronics[6] and bioactive compounds; for example, neuroregulating *N*-arylpiperidines and piperazines.[7] Electrophilic amination of arylmetal reagents represents an alternative approach and thus has attracted considerable interest from synthetic chemists for a long time.[8,9] Although *N*-chloroamines are among the most desirable amination reagents in the alternative amination strategy because of availability and scalability,[10] the classical methods with arylmetal reagents have suffered from severe limitation of substrate scope caused by undesirable elimination reactions and chlorination reactions.[11] Recently, the scope of electro-

[†] International Research Center for Elements Science (IRCELS), Institute for Chemical Research, Kyoto University.

(1) Recent reviews: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (b) Tasler, S.; Lipshutz, B. H. *J. Org. Chem.* **2003**, *68*, 1190–1199. (c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626. (d) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361.

(2) Reviews : (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067. (d) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209.

(3) (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348–1350.

(4) (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.

(5) (a) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829–12842. (b) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029–3036. (c) Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429–1434.

(6) (a) Shirota, Y. *J. Mater. Chem.* **2000**, *10*, 1–25. (b) Mishra, A.; Fischer, M. K. R.; Bäuerle, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 2474–2499.

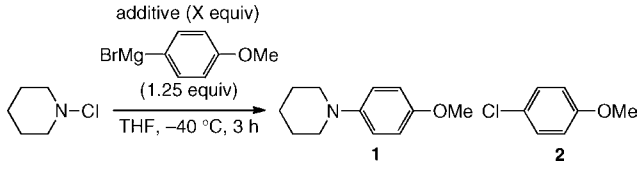
(7) (a) Prisinzano, T. E.; Rice K. C. In *Dopamine Transporters: Chemistry, Biology, and Pharmacology*; Trudell, M. L., Izenwasser, S., Eds.; Wiley & Sons: Weinheim, 2008; pp 211−232. (b) Kharkar, P. S.; Dutta, A. D.; Reith, M. E. A.; Dutta, A. K. In *Dopamine Transporters: Chemistry, Biology, and Pharmacology*; Trudell, M. L., Izenwasser, S., Eds.; Wiley & Sons: Weinheim, 2008; pp 233−264.

(8) Reviews: (a) Chiba, S.; Narasaka, K. In *Amino Group Chemistry. From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2008; pp 1−54. (b) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947–1980. (c) Greck, C.; Genêt, J. P. *Synlett* **1997**, 741–748. (d) Dembech, P.; Seconi, G.; Ricci, A. *Chem.—Eur. J.* **2000**, *6*, 1281–1286. (e) Watson, I. D. G.; Yudin, A. K. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 906–917.

10.1021/ol100235b
Published on Web 03/11/2010

philic amination has been extended by using transition metal catalysts: a copper-catalyzed amination of arylboronic acid with *N*-aryl-*N*-chloroamides[12] and a nickel-catalyzed amination of diarylzinc with *N*,*N*-dialkyl-*N*-chloroamines.[13] Nonetheless, development of a simple and effective aromatic amination without hazardous transition metals can contribute to practical syntheses of the above-mentioned functional arylamines. Herein, we report a transition-metal-free electrophilic amination[14] between aryl Grignard reagents and *N*,*N*-dialkyl-*N*-chloroamines with the aid of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as a key additive.

Table 1. Effect of Coordinative Additives

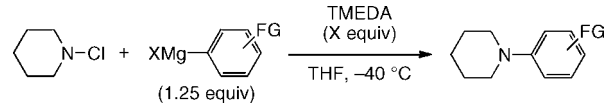


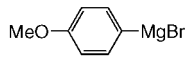
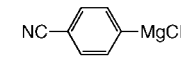
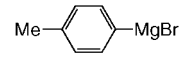
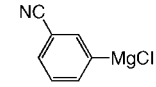
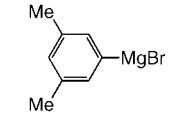
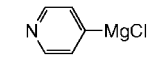
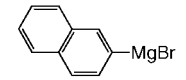
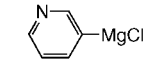
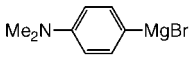
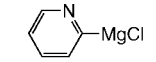
entry[a]	additive (X equiv)	yield of **1**[b] (%)	yield of **2**[b] (%)
1	none (−)	16	46
2	TMEDA[c] (1.5)	50	24
3	TMEDA (3.0)	65	15
4	TMEDA (5.0)	76	7
5	TMPDA[d] (5.0)	30	31
6	DABCO[e] (5.0)	14	15
7	HMTA[f] (5.0)	1	21
8	PMDTA[g] (5.0)	4	8
9	DME[h] (5.0)	17	31

[a] Reactions were carried out on a 0.5 mmol scale. [b] The yield was determined by GC analysis by using undecane as an internal standard. [c] *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine. [d] *N*,*N*,*N*′,*N*′-Tetramethylpropanediamine. [e] Diazabicyclo[2.2.2]octane. [f] Hexamethylenetetramine. [g] *N*,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine. [h] 1,2-Dimethoxyethane.

We conducted the reaction of 1-chloropiperidine and *p*-methoxyphenylmagnesium bromide at −40 °C for screening of additives (Table 1). Without any additives, the reaction proceeded sluggishly to give 1-(4-methoxyphenyl)piperidine **1** in 16% yield via substitution at the nitrogen atom and 1-chloro-4-methoxybenzene **2** in 46% yield via substitution at the chlorine atom (entry 1). Addition of 1.5 equiv of TMEDA considerably improved the yield of **1** (50%) and suppressed the undesirable formation of **2** (24%, entry 2). Further improvement has been achieved by using 3.0 and 5.0 equiv of TMEDA (65 and 76% yields, respectively, entries 3 and 4). *N*,*N*,*N*′,*N*′-Tetramethylpropanediamine (TMPDA) was not as effective as TMEDA (entry 5). Other amines, diazabicyclo[2.2.2]octane (DABCO), hexamethylenetetramine (HMTA), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA), and 1,2-dimethoxyethane (DME) did not improve the product yield (entries 6−9). In the following studies, we thus chose TMEDA as the additive.

Table 2. Scope of Arylmagnesium Reagents



entry[a]	nucleophile	yield (%)[b] (X equiv)	entry[a]	nucleophile	yield (%)[b] (X equiv)
1		76 (5.0)	6[c]		80 (5.0)
2		91 (1.5)	7[c]		92 (5.0)
3		89 (1.5)	8[c]		95 (6.0)
4		93 (1.5)	9[c]		88 (6.0)
5		66 (5.0)	10[c]		65 (6.0)

[a] Reactions were carried out on a 0.5−25 mmol scale. [b] Isolated yield. [c] 1.5 equiv of Grignard reagent was used. Grignard reagent was prepared from the corresponding aryl bromide and *i*-PrMgCl·LiCl.

Table 2 illustrates the scope of arylmagnesium reagents in the reaction with 1-chloropiperidine at −40 °C. The reaction of *p*-methoxyphenylmagnesium bromide gave the desired amination product in 76% yield (entry 1). *p*-Tolyl-, 3,5-dimethylphenyl-, and 2-naphthylmagnesium bromides showed higher selectivity even with reduced amounts of TMEDA to give the corresponding arylpiperidines in 91, 89, and 93% yields, respectively (entries 2−4). The reaction can also be conducted at 0 °C, although slightly lower yield and selectivity were observed (see the Supporting Information).

(9) Copper-mediated reaction: (a) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620–5623. (b) Greck, C.; Bischoff, L.; Ferreira, F.; Genet, J. P. *J. Org. Chem.* **1995**, *60*, 7010–7012. (c) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005–3008. Copper-catalyzed reactions: (d) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681. (e) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364–366. (f) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219–224. (g) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521–1524. Nickel-catalyzed reaction: (h) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799–1801.

(10) *N*-Chloroamines can be prepared by treating the corresponding amines with NaClO or NCS. See: (a) Zhong, Y.; Zhou, H.; Gauthier, D. R., Jr.; Lee, J.; Askin, D.; Dolling, U. H.; Volante, R. P. *Tetrahedron Lett.* **2005**, *46*, 1099–1101. (b) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043–5045.

(11) (a) Coleman, G. H. *J. Am. Chem. Soc.* **1933**, *55*, 3001–3005. (b) Coleman, G. H.; Yager, C. B.; Soroos, H. *J. Am. Chem. Soc.* **1934**, *56*, 965–966. (c) Coleman, G. H.; Hermanson, J. L.; Johnson, H. L. *J. Am. Chem. Soc.* **1937**, *59*, 1896–1897. (d) Coleman, G. H.; Blomquist, R. F. *J. Am. Chem. Soc.* **1941**, *63*, 1692–1694. (e) Yamada, S.; Oguri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1972**, 623a. (f) Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 167–172. (g) Sinha, P.; Knochel, P. *Synlett* **2006**, 3304–3308.

(12) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414–6417.

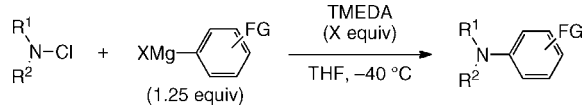
(13) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598–15599.

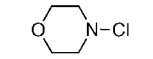
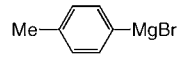
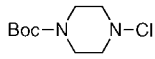
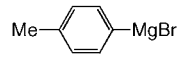
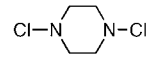
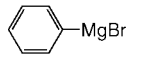
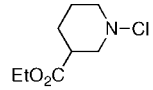
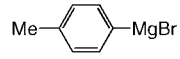
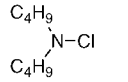
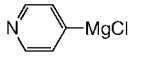
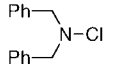
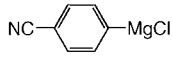
(14) Transition-metal-free nucleophilic aminations: (a) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515–3517. (b) Xu, G.; Wang, Y.-G. *Org. Lett.* **2004**, *6*, 985–987. (c) Bolliger, J. L.; Frech, C. M. *Tetrahedron* **2009**, *65*, 1180–1187.

The dimethylamino group did not interfere with the reaction (entry 5). Mesitylmagnesium bromide did not give the desired product under the reaction conditions, suggesting that the nucleophile substitution reaction is inherently sensitive to steric demands.

The mild reaction conditions allow the participation of functionalized Grignard reagents:[15] 4-cyano- and 3-cyanophenylmagnesium chlorides gave the corresponding aniline derivatives in 80 and 92% yields, respectively (entries 6 and 7). A variety of pyridinylmagnesium chlorides also took part in the reaction (entries 8−10). It is noteworthy that a simple acid−base treatment of the reaction mixture can give analytically pure products (see the Supporting Information).

Table 3. Scope of *N*-Chloroamines



entry[a]	*N*-chloroamine	nucleophile	yield (%)[b] (X equiv)
1			88 (3.0)
2			84 (3.0)
3[c]			78 (10)
4			89 (1.5)
5[d]			78 (6.0)
6[d]			49 (6.0)

[a] Reactions were carried out on a 0.5 or 1.0 mmol scale. [b] Isolated yield. [c] 2.5 equiv of Grignard reagent was used. [d] 1.5 equiv of Grignard reagent was used. Grignard reagent was prepared from the corresponding aryl bromide and *i*-PrMgCl·LiCl.

The present amination reaction is applicable to a variety of *N*-chloroamines (Table 3). 4-Chloromorpholine and 1-Boc-4-chloropiperazine smoothly reacted with *p*-tolylmagnesium bromide at −40 °C to give the corresponding arylamines in 88 and 84% yields, respectively (entries 1 and 2). Double arylation of 1,4-dichloropiperazine took place by using 2.5 equiv of phenylmagnesium bromide to give 1,4-diphenylpiperazine in 78% yield (entry 3). An ethoxycarbonyl group remained intact under the reaction conditions (entry 4). The reaction of acyclic dibutylchloroamine and pyridin-4-ylmagnesium chloride gave the desired product in 78% yield (entry 5). Dibenzylchloroamine, a synthetic equivalent of NH_2^+, can also participate in the reaction (entry 6).

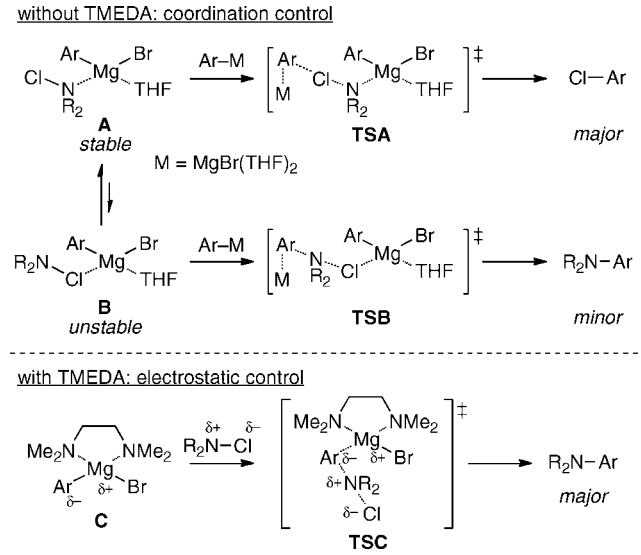


Figure 1. Postulated role of TMEDA.

Figure 1 shows the postulated role of TMEDA in the present reaction. In the absence of TMEDA, arylmagnesium bromide and *N*-chloroamine can form nitrogen-coordinated complex **A** and chloride-coordinated complex **B**, which would give rise to both electrophilic chlorination and amination of Grignard reagent via **TSA** and **TSB**, respectively. DFT calculations[16] suggest that complex **A** is 8.5 kcal/mol more stable than **B** (ΔE), which can account for the dominant formation of the aryl chloride in entry 1, Table 1. In the presence of TMEDA, arylmagnesium bromide forms complex **C**, which has no vacant coordination site for *N*-chloroamine. The amination, thus, can take place predominantly via **TSC**, which can be stabilized by electrostatic interaction between the negatively charged chloride atom of *N*-chloroamine and the magnesium atom (entries 2−4, Table 1).

In summary, we have developed an efficient aromatic carbon−nitrogen bond-forming reaction between aryl Grignard reagents and *N*-chloroamines with the aid of TMEDA. The features of the present method are as follows: high-yielding, chemoselective, and free from transition metals. The simple and scalable procedure is suitable for large-scale production of *N*-arylpiperidines and piperazines as well as various aniline derivatives as drug and agrochemical intermediates.

(15) Preparation of Grignard reagents from aryl bromides with *i*-PrMgCl·LiCl: Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336.

(16) Phenylmagnesium bromide, *N*-chloropiperidine, and tetrahydrofuran (THF) were chosen as a chemical model. The DFT method was employed using the B3LYP hybrid functional and the 6-31G* basis set. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986 and references cited therein. Details are described in the Supporting Information.

Acknowledgment. This work was partially supported by Grant-in-Aids for Scientific Research on Priority Areas "Synergistic Effects for Creation of Functional Molecules" (M.N., 18064006) and "Chemistry of Concerto Catalysis" (T.H., 20037033) and Grant-in-Aids for Young Scientists (S, M.N., 2075003; B, T.H., 2175098), and Global COE Program "International Center for Integrated Research and Advanced Education in Materials Science" from JSPS and MEXT. Financial support from the Uehara Memorial Foundation and Tosoh Organic Chemical and Finechem Corps. is gratefully acknowledged. We also thank Mr. Y. Hanasaki (Tosoh Organic Chemical Co.) for bringing the industrial importance of *N*-arylation to our attention.

Supporting Information Available: Experimental procedures and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100235B